ORIGINAL ARTICLE

“Lambda-wave” ST-elevation is associated with severe prognosis in stress (takotsubo) cardiomyopathy

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Abstract

Background: Persistent ST-segment elevation in acute coronary syndrome is associated with both short and long-term complications. By contrast, there is limited information about ST-elevation and its evolution during takotsubo (stress) cardiomyopathy (TTC).

Aim: To evaluate whether persistent downsloping ST-elevation in the early stages of TTC might correlate with short and long-term clinical events.

Methods: One-hundred fifty-eight consecutive subjects with TTC were prospectively enrolled and assessed by electrocardiogram. Patients were classified in two groups according to the presence of downsloping ST-elevation ≥ 5 mm lasting at least 24 hr (“lambda-wave” ST-elevation group vs. without downsloping ST-elevation) in at least one/two contiguous leads.

Results: Five (3.2%) patients, all female with a mean left ventricular ejection fraction $32 \pm 5\%$, were included in the lambda-wave ST-elevation group. These patients were characterized by a higher prevalence of physical stressor (100% vs. 49%, $p = 0.04$) and higher admission and peak levels of troponin-I levels during hospitalization. Peak of ST-elevation in the lambda-wave ST-elevation group was reached 6 hr after admission and gradually decreased after 24 hr. In-hospital complications were observed in all the patients presenting lambda ST-elevation (100% vs. 23%, $p = 0.03$, OR: 29.1, $p = 0.04$); one patient presented endoventricular thrombosis and two died of cardiogenic shock. At long-term follow-up (mean 443 days), adverse events were observed in 80% of patients with lambda-wave ST-elevation (RR of adverse events at follow-up 32, $p < 0.01$).

Conclusion: Persistent downsloping lambda-wave ST-elevation during the acute phase of stress cardiomyopathy may be associated with a higher risk of adverse events at short and long-term follow-up.

KEYWORDS

ECG, follow-up, lambda-wave, ST-elevation, stress cardiomyopathy, takotsubo

1 | INTRODUCTION

Takotsubo-(stress)-cardiomyopathy (TTC) is a form of acute and transient ventricular dysfunction affecting mostly postmenopausal women after either a physical or an emotional stress, secondary to sympathetic hypertone provoking heart stunning. The usual distinctive characteristics are the left ventricle ampoule appearance due to akinesia of apex and mid-ventricle associated with basal hyperkinesia, and the absence of coronary plaque rupture at coronary angiography. Several pathogenetic mechanisms have been hypothesized (coronary spasm, catecholamine toxicity and microcirculation dysfunction) (Akashi, Nef, & Lyon, 2015; Warisawa, Naganuma, & Nakamura, 2016), albeit the leading mechanism is not yet completely clear.

Electrocardiogram signs of TTC (ST-elevation, negative T-waves) may also resemble acute coronary syndrome (ACS), although “mirrored” ST-segment depression is quite uncommon in TTC (Frangieh et al., 2016; Sharkey et al., 2008). Rule-out algorithms have been proposed to distinguish ST-elevation in ACS from TTC (Frangieh et al., 2016); however, they present very low sensitivity and negative predictive value and therefore imaging examination is still essential for a final diagnosis of TTC.

The presence of persistent ST-segment elevation after both percutaneous or pharmacological revascularization is strongly associated with complications and a poor prognosis (van der Zwaan et al., 2010). Lambda-wave ST-elevation, after the Greek letter λ because of the triangular shape of the ST-segment, has been occasionally reported in subjects incurring fatal arrhythmias and sudden cardiac death either primarily or secondary to ischemic condition (Gussak, Bjerregaard, & Kostis, 2004; Kukla, Jastrzebski, Sacha, & Bryniarski, 2008), and also in TTC (Birnbaum & Nikus, 2016).

Less is known about the prognostic role of persistent lambda-wave ST-elevation and its evolution in patients with TTC; the aim of the present study was therefore to evaluate the prognostic value of persistent downsloping ST-elevation during the acute phase of TTC.

2 | METHODS

2.1 | Study population

We prospectively enrolled 158 consecutive patients who fulfilled the revised Mayo Clinic diagnostic criteria for TTC (Madhavan & Prasad, 2010) at the Department of Cardiology, University Hospital “Ospedali Riuniti”, Foggia, Apulia, Italy, between July 2007 and March 2017. All patients provided a written informed consent and the study was approved by local ethical committee.

2.2 | Inclusion criteria

The lambda-wave pattern was defined according to the following features: (a) a steep upslope coinciding with the ascending branch of the R wave; (b) a slurrier downsloping limb; (c) a minimum deviation of ≥ 5 mm; (d) a preceding depolarization as QR, qR and rSR', without

a distinct J point, which is instead essential to identify ST-segment elevation (Rautaharju et al., 2009).

Patients presenting with the abovementioned characteristics lasting at least 24 hr in at least two contiguous leads were included in the lambda-wave ST-elevation group and compared with the other subjects enrolled in the study.

2.3 | Exclusion criteria

Patients either presenting other nondownsloping ST-elevation, pacemaker-dependent subjects, patients with electrocardiographic signs of left ventricular hypertrophy and/or permanent intraventricular conduction disturbances were not included in the lambda-wave ST-elevation group.

2.4 | Clinical examination and echocardiography

All patients underwent clinical examination; age, gender, medical history, and kind of stressors were recorded. Stressors were classified into emotional or physical (due to another medical illness). A two-dimensional color-Doppler echocardiographic examination on the day of admission, on the third, the fifth and the discharge day was performed to assess ventricular function, presence of mitral leaflet systolic anterior movement (SAM), left ventricular outflow obstruction (defined as at least a pressure gradient of 30 mmHg using PW Doppler at rest), pericardial effusion, echo-contrast, or thrombosis. The left ventricular ejection fraction (LVEF) was calculated using the Simpson method from the apical four and two-chamber views.

2.5 | Blood tests

Blood tests were obtained by venipuncture in order to measure circulating levels of cardiac troponin-I (TnI), C-reactive protein (CRP), and NT-pro-BNP (N-terminal-pro-Brain Natriuretic Peptide) at the admission, and then daily until discharge. The upper limit of normal for apparently healthy persons (95th percentile) was 100 pg/ml for NT-pro-BNP, 5 mg/dl for C-reactive protein, and <0.5 ng/ml for troponin-I.

2.6 | Electrocardiogram analysis

Twelve-leads electrocardiograms (ECG) were routinely recorded from the admission to the discharge day (recording speed of 25 mm/s and amplification of 10 mm/mV). All patients underwent ECG recording before and after coronary angiography. Patients with lambda-wave ST-elevation underwent electrocardiogram examination every 2 hr for the first 24 hr and then daily until discharge. With this aim, red-dots were not displaced from the original positions on the chest during the whole monitoring. ECG details including cardiac rhythm, ST and T-wave changes, QT and QTc intervals were recorded. ST-segment elevation was defined as shift ≥ 0.1 mV in all leads from the J point in at least two contiguous leads, except in V2–V3 where ≥ 0.15 mV was used both in males and in females (since women constituted the majority of the study population),

meanwhile ST-depression was indicated if it was ≥ 0.1 mV at the J-point in at least two contiguous leads, except in V2–V3 where it was ≥ 0.05 mV (Thygesen et al., 2012). If the J point was not easily identifiable, as in most of the cases, the subsequent TP segment (indicating the isoelectric line) was conventionally employed as reference marker. QTc was calculated from the longest QT interval measured among all leads and T-wave changes were considered present if the depth was 0.1 mV in any lead. The ECG data were analyzed independently by two operators (N. T. and F. G.) in a blinded manner.

2.7 | Follow-up and definition of outcome

Patients were scheduled for clinical and echocardiographic examinations at the outpatient clinic (3 months after TTC episode and every 9 months). For patients with poor compliance to outpatient visits, phone calls were made to determine recurrence and incidence of clinical outcomes.

Clinical endpoints (in-out of hospital complications) were classified according to World Health Organization classification of disease (ICD-Code 2016; <http://apps.who.int/classifications/icd10/browse/2016/en>). Recorded in-hospital complications were: death (R96-98-99), cardiogenic shock (R57.0), pulmonary edema (J81), stroke (I64), cardiac arrhythmia, unspecified (I49.9) intracardiac thrombosis, not elsewhere classified (I51.3), acute renal failure (N17); as out of hospital complications re-hospitalization for TTC recurrence (I51.81), heart failure (I50), stroke (I64), cardiac arrhythmia, unspecified (I49.9), malignant neoplasm, primary site unspecified (C80.9), and death (R96-98-99) were evaluated.

2.8 | Statistical analysis

Continuous variables were reported as mean $\pm$ standard deviation, and categorical variables were expressed as proportions; groups were compared with paired, unpaired *t* test or chi-squared test.

Logistic regression analysis was used to calculate odds ratio for the incidence of adverse events during hospitalization with a 95% confidence interval (95% CI). Kaplan–Meier plots were used to display survival event-free curves and analyzed with Log-Rank test. Cox regression analysis was used to calculate relative risk of adverse events at follow-up.

Multivariable analysis was used to corrected results for principal confounders. A *p* value < 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Patients' characteristics

Five (3.2%) patients, all women, mean LVEF $32 \pm 5\%$, were included in the lambda-wave ST-elevation group. There were no statistically significant differences in term of age, admission and discharge LVEF and cardiovascular risk factors between the lambda-wave ST-elevation group and the control group. Patients with lambda-wave ST-elevation were characterized by higher prevalence of physical stressor (100%

vs. 49%, $p < 0.05$), higher levels of admission and peak troponin-I during hospitalization (35 ± 42 vs. 5 ± 12 ng/L, 40 ± 43 vs. 5 ± 13 ng/L, $p < 0.01$; Table 1). Moreover, four patients out of five were affected by cognitive impairment of various degree (80% vs. 24%, $p = 0.05$) known before the acute event, and one of these had sequelae of previous right-sided ischemic stroke with left hemiplegia.

3.2 | Electrocardiographic features of the lambda-wave ST elevation group

Mean peak of ST-elevation was overall reached 6 hr after admission; ST-segment gradually normalized 48 hr thereafter (Figure 1). R-wave drop and ST-segment depression were missing in all lambda-wave electrocardiograms. During hospitalization, the lambda-wave electrocardiograms were characterized by mild QT-prolongation (415.6 ± 55.7 ms at admission vs. 455 ± 65 ms at discharge, $p = 0.39$); ST-elevation was gradually followed by diffuse T-wave inversion in four out of five patients.

3.3 | Coronary angiography findings

Coronary angiography imaging showed patent coronary arteries in all patients with the lambda-wave ST-elevation. However, tortuous coronary arteries defined as ≥ 3 consecutive curvatures $\geq 90^\circ$ or by ≥ 2 consecutive curvatures $\geq 180^\circ$ (Arcari et al., 2017), were found in four out of five patients, involving prevalently the left anterior descending (LAD) coronary artery (60% of cases; Table 2). Wrap-around LAD was identified in two patients, one of which incidentally presented also a coronary-ventricular fistula (a diastolic “blow” effect of medium contrast from the distal LAD into the left ventricular chamber; Figure 2).

3.4 | In-hospital outcomes

Mean hospital stay in the lambda-wave ST-elevation group was 8.6 ± 5.4 days (vs. 8.1 ± 3.6 , $p = 0.77$). All patients with the lambda-wave pattern incurred complications within 48 hr after admission (OR: 29.1, 95% CI: 1.1–782.4, $p = 0.04$, Table 3). One patient presented endoventricular thrombosis, treated with oral anticoagulation. Four patients (80%) experienced cardiogenic shock by 2 days after admission requiring inotropic support in addition to noninvasive ventilation (BPAP modality) in three of them (Table 2). Two of these patients died of refractory cardiogenic shock complicated by acute renal failure, respectively after 3 and 5 days from the admission; the latter also experienced intraventricular obstructive gradient (> 50 mmHg), with systolic anterior movement and one episode of self-limiting torsade de pointes. The remaining two patients were discharged within 10 days without any sequelae.

3.5 | Follow-up outcomes

At long-term follow-up (mean 442 ± 565 days), one patient died because of noncardiovascular cause (colon cancer) 5 months after TTC episode, while another patient was hospitalized for acute heart failure 10 days after discharge. Incidence of adverse events at follow-up

TABLE 1 Patients' characteristics

	Mean		Mean		p
	Lambda-wave (N 5)	SD	Control group (N 153)	SD	
Age	81	6	74	12	0.2030
Male	0%		12%		0.4041
Hypertension	80%		78%		0.90
Diabetes	40%		26%		0.47
Neurological disease	80%		24%		0.05
Pneumological disease	40%		27%		0.52
No chest pain	60%		30%		0.15
Emotional stressor	0%		25%		0.19
Physical stressor	100%		49%		0.04
No stressor	0%		28%		0.16
Admission LVEF	32%	5%	36%	9%	0.33
Mitral regurgitation	1.6	1.1	1.1	0.7	0.16
RV dysfunction	0%		6%		0.58
LVOTO	20%		14%		0.53
Admission ECG features:					
Negative T waves	0%		56%		0.02
ST-elevation	100%		48%		0.04
ST-depression	0%		4%		0.68
QT-prolongation	0%		37%		0.19
Admission CRP (mg/dl)	110	58	118	41	0.71
Admission NT-PRO-BNP (pg/ml)	15,203	7,047	13,979	14,917	0.87
Admission Tnl (ng/ml)	34.8	41.9	4.6	12.4	<0.01
Peak Tnl (ng/ml)	39.8	43.4	4.9	12.5	<0.01
Events during hospitalization	100%		23%		0.03
Death	40%		7%		0.05
Pulmonary edema	25%		11%		0.36
Stroke	0%		1%		0.81
Invasive ventilation	50%		9%		0.01
Events at follow-up	80%		21%		0.01

Note. CRP: C reactive protein; LVEF: left ventricular ejection fraction; LVOTO: left ventricular outflow tract obstruction; NT-pro-BNP: N-terminal pro-brain natriuretic peptide; RV: right ventricle; Tnl: cardiac troponin I. Statistically significant values are in bold type.

was significantly higher in subjects with lambda-wave ST-elevation (Log-Rank $p < 0.01$). Mortality rates at 180 days are given in Figure 3 (Log Rank $p < 0.01$). The relative risk of adverse events at follow-up was 32 (95% CI: 7–154, $p < 0.01$, Table 4), significant even after correction for principal confounders.

4 | DISCUSSION

To the best of our knowledge, this is one of the first series of peculiar electrocardiographic findings, represented by downsloping ST-elevation resembling the ancient Greek letter λ , during the acute phase of TTC. The main findings of the study are as follows:

1. 3.2% of patient with TTC presented a severe downsloping ST-elevation (with the lambda-wave pattern) during the first 24 hr after admission;
2. Patients with this ECG pattern experienced TTC mainly after a physical stressor and were characterized by a high prevalence of preexisting cognitive impairment;
3. A higher prevalence of in-hospital and at follow-up complications was found in patients with the lambda-wave ST-elevation pattern.

The role of the ECG in stress cardiomyopathy diagnosis and prognosis is still debated (Frangieh et al., 2016; Madias, 2015; Sharkey et al., 2008). The lambda-wave pattern in TTC is not only remarkable for its high voltage, its morphology and its localization (Figure 4), but also for

its temporal course, characterized by progressive downsloping ST-segment elevation peaking within the first day and with a subsequent slow decrease.

4.1 | ST-elevation in acute transmural myocardial ischemia

ST-elevation in transmural ischemia is explained by two concurrent theories, one representing ST-elevation as the tangential current from the normal surrounding tissue to the ischemic area, another based on the “transmural electrophysiologic gradient”, able to produce a current perpendicular to the heart surface from the endocardium to the

epicardial layer (Di Diego & Antzelevitch, 2014). Basically, low oxygen supply may be responsible for several electrophysiological perturbations; the Na^+/K^+ pump is strictly dependent on ATP availability, which in turns derives from aerobic metabolism. When oxygen supply is reduced, the pump fails to function leading to an accumulation of intracellular Na^+ and activation of others ionic channels ($\text{Na}^+/\text{Ca}^{++}$ exchanger, and ATP-dependent- K^+ channels responsible for intracellular calcium overload, and potassium outflow with further calcium entry), which eventually depolarizes the ischemic tissue (more positively charged), and therefore the current flows from the normal surrounding cells toward the ischemic area. However, in the same ischemic zone, the epicardial cells have a shorter action potential because of low sodium entrance and increased potassium outflow, thus making the extracellular space more electropositive; thus, the current flows perpendicularly from the inner to the outer layer of the ischemic area (Di Diego & Antzelevitch, 2014). In both cases, the surface electrode records an approaching current, equivalent to the ST-segment elevation.

FIGURE 1 ST-segment voltage during first 48 hr of hospitalization among patients with lambda-wave ST elevation pattern

4.2 | Possible mechanism of ST-elevation in TTC

ST-elevation in TTC could be hypothetically explained by three complementary and overlapping physiopathologic factors: ischemia, mechano-electric effect due to wall motion abnormalities, and neurovegetative modulation. Madias previously proposed two possible mechanisms for ST-elevation in TTC, one, ischemic, and another “neuro-mechanical”, referring to the persistent ST-elevation as in dyskinetic postinfarction aneurysms (Madias, 2013). ST-segment elevation is usually present in about 56% of TTC cases and its amplitude is usually lower than in anterior STEMI (Frangieh et al., 2016; Madias, 2015; Parkkonen et al., 2014). Presumably, in the absence of any sign of vasospasm, tortuous

TABLE 2 Clinical characteristics of lambda-wave group

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Chief symptom	Chest discomfort	Fatigue	Chest discomfort	Dyspnea	Dyspnea
Stressor	Subocclusive fecaloma	C. Difficile diarrhea	Pneumonia and fever	Femoral fracture	Pneumonia and fever
Admission systolic BP (mmHg)	110	120	135	160	105
Lambda-wave localization	V1-V3	V2-V6	V2-V5	V2-V6	V1-V6
Highest ST-elevation (mV)	1 in V2	0.5 in V4	1.9 in V3	2 in V2	1.4 in V3
Tortuous coronary	LAD, ^a LCX, RC	None	LAD	LAD	LCX, RC
Cardiogenic shock/ systolic BP (mmHg)	Yes/65	None ^b	Yes/70	Yes/90	Yes/80 ^c
Inotropic agent used	D	None	D + N	D	D + N
Noninvasive ventilation (BPAP)	Yes	None	Yes	None	Yes
TnI peak (mg/dl)	6.49	69.03	13.16	6.29	8.51

Notes. D: dopamine; LAD: left anterior descending; LCX: left circumflex; N: noradrenaline; RC: right coronary artery.

^aThe patients presented a wrap-around coronary-ventricular fistula.

^bThe patient developed endoventricular thrombosis.

^cThe patient developed intraventricular gradient with systolic anterior movement of mitral leaflet (SAM) and also a torsade de pointes.

coronary anatomy may be also partly responsible for distal ischemia in our patients, as a recent retrospective case-control study showed about relation between TTC and coronary abnormalities (Arcari et al., 2017). Catecholamine surge may precipitate ischemia by increasing myocardial metabolic demand, and may compromise the blood flow in tortuous vessels, as illustrated in computational, in vivo and in vitro models (Han, 2012; Xie, Wang, Zhu, Zhou, & Zhou, 2013). Local intermittent microvascular constriction, maybe induced by neuropeptide-Y released from sympathetic fibers, may also not be excluded (Yalta, Sivri, & Yalta, 2011). Thus, the sum of the cited mechanisms may justify for the lambda-like ST-elevation. As it identifies an extreme grade of ischemia (grade IV according to Sclarovsky-Birnbaum score) (Birnbaum & Nikus, 2016), the ischemic pathogenesis of the lambda-wave ST-elevation could be taken into account.

4.3 | ST-elevation morphology and localization: plausible explanations

It is also noteworthy the ST-segment shape observed in this study. Ischemic ST-elevation is generally convex and, in the early phases,

the convexity may be fused with R wave providing the “tomb-stone-like” pattern. In Brugada syndrome, instead, the “coved-type” ST-pattern is mainly caused by a transmural voltage gradient due to a mismatch in repolarization duration between the epicardium and the endocardium on genetic bases (Kurita et al., 2002). Thus, the lambda-wave pattern can be ideally assimilated to an extreme “coved-type” pattern, perhaps related to transmural differences in myocardial repolarization. In nonischemic animal models, transmural systolic wall tension gradient can influence action potentials (the mechano-electric feedback) to such an extent to provoke epicardial early repolarization, and an endo-epicardium voltage gradient resulting in ST modification (Shimada et al., 1997) (Figure 5). For this reason, ST-elevation was not diffused in our patients, but localized predominantly in anterior-apical zone (mostly in V2–V4), where the apical ballooning systolic tension was probably higher because of apical dysfunction. Similarly, ventricular edema is thought to correlate with the amplitude and the localization of negative T waves in TTC (Perazzolo Marra et al., 2013).

On the other hand, sympathetic system hyperactivation may be also found in TTC (Ortak et al., 2009) and can influence

FIGURE 2 Angiography showing tortuous coronaries and typical apical ballooning of the left ventricle. Green arrows indicate coronary-ventricular fistula in a patient with wrap-around LAD

	Odds ratio	95% lower	95% upper	<i>p</i>
Lambda-wave ST-elevation	29.1	1.1	782.4	0.04
Age (years)	1.1	1.0	1.1	0.05
Male	3.2	0.9	11.0	0.06
Admission left ventricular ejection fraction	0.0001	<0.0001	0.03	0.01
Admission troponin	0.9	0.9	1.0	0.23

Note. Statistically significant values are in bold type.

TABLE 3 Odds ratio for the incidence of in-hospital complications

repolarization and hence the ECG (Shen & Zipes, 2014; Y-Hassan, 2015). A recent work showed that transmural dispersion of repolarization does not increase after cervical ganglia stimulation (Yagishita

FIGURE 3 Kaplan Meier mortality curves at follow-up (Log-Rank $p < 0.001$)

TABLE 4 Multivariable Cox' regression analysis with predictors of adverse events at follow-up

	Risk ratio	95% lower	95% upper	<i>p</i>
Lambda-wave ST-elevation	32.40	6.81	154.09	<0.01
Age (years)	1.04	0.997	1.076	0.06
Male	3.54	1.48	8.46	0.04
Admission left ventricular ejection fraction	0.18	0.001	26.49	0.41
Admission troponin	0.98	0.95	1.01	0.11

Note. Statistically significant values are in bold type.

et al., 2015); however, a regional electrical gradient between the posterior and the anterior wall, caused by a greater shortening of action potentials in the anterior wall, may result in ST-elevation in anterior leads during right stellate ganglion stimulation, which is exactly the ganglion activated under stressful circumstances (Jovanovic, Spasojevic, Stefanovic, & Dronjak, 2014; Mehta, Jain, & Mehta, 1999).

4.4 | Potential hypothesis for the temporal pattern evolution

Another finding of the lambda-wave pattern is its evolution over time (Figures 1 and 4). The ST magnitude in the involved leads presented significant variations throughout the in-hospital stay, with a peak between 6 and 12 hr in all patients and a full normalization after the second day. Rapid evolution can be partly explained by direct correlation between preload changes, caused by diuretic therapy, as ST-elevation in nonischemic models (Shimada et al., 1997). The mean peak after

FIGURE 4 Lambda-wave ECG pattern evolution from the admission to the discharge in two patients (a,b). Please note that a mild transient axis deviation (from -30° up to $+15^\circ/+30^\circ$) appeared in the (a)

about 6 hr might reflect the norepinephrine half-life in stress conditions (normally 8–12 hr) (Eisenhofer, Kopin, & Goldstein, 2004), and the duration of approximately 48 hr is consistent with the vaso-constrictive neuropeptide-Y levels, which was shown to diminish after 2 days in a TTC patient with ST-elevation in anterior leads (Szardien et al., 2011; Yalta et al., 2011).

4.5 | Potential combination of preexisting neurological disease and physical stressor

Since the prevalence of senile dementia in the lambda-wave ST-elevation group was higher and preexisting cognitive decline was known in the four women with cardiogenic shock before the acute event, dementia might be considered an additional risk factor in TTC (Santoro et al., 2013). In fact, patients with Alzheimer's disease present signs of silent autonomic dysfunction as suggested by spontaneous hypotension in the supine position, or low blood pressure response to Valsalva maneuver caused by central and peripheral nervous autonomic system impairment (Giubilei et al., 1998; Jensen-Dahm et al., 2015; Novak, Novak, Li, & Remillard, 1994). Furthermore, abnormal cardiac repolarization (measured as T-wave nondipolar voltage) is probably associated with altered

global cognitive performance, thus partly accounting for electrocardiographic abnormalities in our patients (Lucas, Mendes de Leon, Prineas, Bienias, & Evans, 2010).

Finally, we observed a relevant prevalence of physical stressors in the lambda-wave pattern group (100% vs. 49% controls, $p < 0.05$), whereas the largest registry reports 36% prevalence of physical causes (Templin et al., 2015). In this regard, we also may hypothesize that the response to a medical acute disease is notably expressed in such patients, perhaps because of the deep loss of the central control on the sympathetic fight and fly reflex, compared to subjects with normal neurologic status (Aharon-Peretz, Harel, Revach, & Ben-Haim, 1992; Mendez, Joshi, Daianu, Jimenez, & Thompson, 2015; Toledo & Junqueira, 2010). Consequently, the extent of such adrenergic response translates into a more evident cardiovascular reserve impairment, as discussed by Song et al. (2012), who already illustrated that physical stressors per se were linked to higher prevalence of cardiogenic shock, inotropes use, and lower LVEF.

4.6 | Clinical implications

Identification of predictive factors in TTC patients has been evaluated in several studies and could be helpful to guide management

FIGURE 5 Mechano-electric feedback, a possible patho-physiology explanation for ST-elevation in non-ischemic tissue. SAC: stressed activated channels

strategies. Clinical characteristics including age, male gender, the presence of physical triggers (secondary TTC) (Nunez-Gil et al., 2016; Song et al., 2012 Nov), and serum biomarkers (neoplastic marker CA-125, interleukins 6 and 10, and estimated glomerular filtrate rate) (Santoro, Ferraretti, Ieva, et al., 2016; Santoro, Ferraretti, Musaico, et al., 2016; Santoro, Tarantino, et al., 2016) are linked to adverse outcome. In this study, gender and lambda-wave ST-elevation were related to adverse event at follow-up. Moreover, we found that troponin-I levels, were significantly increased among patients with lambda-wave pattern. The amount of admission and peak Tnl values presumably matches the myocardial damage directly derived from the excessive catecholamine levels, and may reflect the extent of impaired myocardial tissue, whose most evident manifestation is the ST-segment elevation. Additionally, our group has recently found that several ECG findings may have a prognostic role in TTC as persistent ST elevation for more than 48 hr and QT prolongation at admission (Santoro et al., 2017, 2018).

According to our data, lambda-wave pattern may identify particularly frail patients deserving a closer clinical monitoring during hospitalization as well as at follow-up.

The real predictive role of such electrocardiogram sign in predicting in-hospital events and long-term clinical outcomes remains to be established in larger populations. Further studies are surely warranted.

5 | CONCLUSIONS

A downsloping ST-elevation lambda-wave may be occasionally observed during the acute phase of TTC. The pattern has a typical time course during the first 24 hr of hospitalization and could be associated with severe complications.

5.1 | Limitations

Several differences are not statistically significant because of the small number of enrolled patients. Electrocardiograms were recorded at the first medical contact, not at the real disease onset.

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DISCLOSURE

No conflict of interest to disclose.

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